MOLECULAR BIOLOGY AND TCGA DATA

Jean-Pascal Machiels

Department of Medical Oncology
Institut Roi Albert II
Cliniques universitaires Saint-Luc
Université catholique de Louvain
Brussels, Belgium
DISCLOSURE OF INTEREST

Advisory role: MSD (uncompensated), Innate, Debio, Astra-Zeneca, Nanobiotix

Research grants: Novartis, Janssen.
Squamous cell carcinoma of the head and neck

The seventh most common form of cancer
600,000 cases per year worldwide

➔ Alcohol & tabacco
(oral cavity, larynx and pharynx)

➔ Human Papillomavirus (HPV+)
(oropharynx)
# Candidate Therapeutic Targets

**Analysis – Tanguy Seiworth, Niki Schultz**

<table>
<thead>
<tr>
<th>Genes</th>
<th>HPV(-) N=244</th>
<th>HPV(+) N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>MET</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>EPHA2</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>DDR2</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>CCND1</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>PIK3</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>TP53</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>99%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Amplification
- Homozygous Deletion
- Heterozygous Deletion
- mRNA Downregulation
- Mutation
- RPPA Downregulation
- RPPA Upregulation
Leemans R et al, Nature Reviews 2011
HPV negative

- DNA damage
- Cyclin A, CDK1
- Cyclin B, CDK1
- Senescence and differentiation
- M, G2, G1, G0, S
- p16
- CDK4 or CDK6
- Cyclin D1
- p21
- Cyclin E, CDK2
- E2F
- RB
- Mitogens

- Mutated in 70%
- Inactivated in 90%
- Amplified in 30%

Leemans R et al, Nature Reviews 2011
HPV positive

Leemans R et al, Nature Reviews 2011
• p16 is a good surrogate marker of HPV infection in oropharyngeal cancer

• Diagnosis and prognosis value of p16 outside the oropharynx is controversial
Presentation outline

• p16 oropharyngeal cancer
• Anti-EGFR therapy and p16
• Other potential targets
• Microenvironment: immunology
Survival by HPV status for oro pharyngeal cancer

**RTOG 0129**

**TROG 02.02**

HR = 0.36, P = 0.004

2-y OS: 74% & 91%

Ang KK NEJM 2015
Rischin JCO 2010
Oropharyngeal cancer: prognosis

T4 or N3 disease
**TNM p16+ oropharyngeal cancer, 8th edition**

<table>
<thead>
<tr>
<th>T CATEGORY</th>
<th>T CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary identified</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or smaller in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor larger than 2 cm but not larger than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N CATEGORY</th>
<th>N CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>One or more ipsilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N2</td>
<td>Contralateral or bilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph node(s) larger than 6 cm</td>
</tr>
</tbody>
</table>

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TNM p16+ oropharyngeal cancer, 8th edition


<table>
<thead>
<tr>
<th>T CATEGORY</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NA</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T2</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T3</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T4</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

*Any M1 is stage IV.

T4 or N3 = stage III
T3 or N2 = stage II
Presentation outline

• p16 oropharyngeal cancer

• Anti-EGFR therapy and p16

• Other potential targets

• Microenvironment: immunology
EGFR expression and prognosis
Radiotherapy +/- cetuximab: stage 3 and 4

Hazard ratio = 0.74 (95% CI: 0.57–0.97)
Log-rank p=0.03

Bonner, Lancet Oncology 2010
**Figure 3: Overall survival by pre-treatment characteristics: 5-year update**

AJCC=American Joint Committee on Cancer. KPS=Karnofsky performance score. EGFR=epidermal growth factor receptor.
p16 positive as a predictive biomarker?

- 3-year LRC rate: 87% vs 65%
- HR: 0.31 (95%, CI, 0.11-0.88)

p16 -:
- 3-year LRC rate: 31 vs 19%
- HR: 0.78 (95% CI, 0.49-1.25)

Rosenthal, J Clin Oncol 2016
Panitumumab + RT versus chemoradiation

Concert 2: Chemoradiation vs radiotherapy plus panitumumab

Mesia et al, Lancet Oncology 2015
Giralt et al, Lancet Oncology 2015
**Panitumumab + RT versus chemoradiation**

Concert 2: **Chemoradiation vs radiotherapy plus panitumumab**

<table>
<thead>
<tr>
<th>2-Y survival</th>
<th>Chemoradiation</th>
<th>RT+ panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>71%</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

Mesia et al, Lancet Oncology 2015
Giralt et al, Lancet Oncology 2015
Panitumumab + RT vs chemoradiation

NCIC CTG HN6
Stage III/IV

Conventional Radiation (70 Gy in 7 weeks)
- Cisplatin 100 mg/m2 Day 1, 22, 43
- N=160

Primary endpoint = PFS

Accelerated Radiation (70 Gy in 6 weeks)
- Panitumumab 9 mg/kg one week before RT and on days 15 and 36
- N=160

L Siu et al. ASCO 2015
Panitumumab + RT vs chemoradiation

NCIC CTG HN6
Stage III/IV

Conventional Radiation (70 Gy in 7 weeks)
Cisplatin 100 mg/m² Day 1, 22, 43
N=160
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Panitumumab 9 mg/kg one week before RT and on days 15 and 36
N=160

L Siu et al. ASCO 2015
Primary Endpoint: PFS

<table>
<thead>
<tr>
<th>Study arm</th>
<th>2-year PFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>76.0%</td>
<td>68 – 82%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>72.8%</td>
<td>68 – 78%</td>
</tr>
</tbody>
</table>

HR 0.95 (95% CI = 0.60 – 1.50)  
Stratified log rank p-value = 0.83

Overall Survival

<table>
<thead>
<tr>
<th>Study arm</th>
<th>2-year OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>88.0%</td>
<td>82 – 92%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>80.5%</td>
<td>74 – 89%</td>
</tr>
</tbody>
</table>

HR 0.89 (95% CI = 0.54 – 1.48)  
Stratified log rank p-value = 0.86

L Siu et al. ASCO 2015
This supports the investigation of treatment de-escalation in favorable HPV positive by replacing chemotherapy with anti-EGFR mAbs
This supports the investigation of treatment de-escalation in favor of HPV positive by replacing chemotherapy with anti-EGFR mAbs.
The activity of anti-EGR therapy in p16+ **recurrent** disease is a different story and will be discussed in the recurrent presentation.
Presentation outline

- p16 oropharyngeal cancer
- Anti-EGFR therapy and p16
- Other potential targets
- Microenvironment: immunology
**HER family**
- *EGFR* amplification/mutation in 15%
- *ERBB2* amplification/mutation in 5%

**FGFR pathway**
- *FGFR1* amplification in 10% HPV neg disease
- *FGFR3* mutations in up to 10% HPV pos disease

**PI3K pathway**
- *PIK3CA* mutation/amplification in up to 56% HPV positive SCCHN
- PTEN loss in up to 12%

**HRAS mutated in 4-5%**
- Homologous recombination deficiency in HPV+ or in HPV- platinum sensitive disease?
HPV negative

- Mutated in 70%
- Amplified in 30%
- Inactivated in 90%

CDK inhibitors: Palbociclib (LEE011, LY2835219)

Leemans R et al, Nature Reviews 2011
Presentation outline

• p16 oropharyngeal cancer
• Anti-EGFR therapy and p16
• Other potential targets
• Microenvironment: immunology
T cell

anti-tumor
T lymphocytes

tumor antigens

Genes encoding tumor antigens:
1. mutated
2. cancer-germline (MAGE)
3. viral
4. differentiation
5. over-expressed
Non-synonymous mutations result in amino acid change in a protein that can be recognized by T-cells.

Vogelstein et al. Science 2013
The cancer-immunity cycle

- Priming and activation (APCs and T cells)
- Cancer antigen presentation (dendritic cells/APCs)
- Trafficking of T cells to tumours
- Infiltration of T cells into tumours (CTLs, endothelial cells)
- Recognition of cancer cells by T cells (CTLs, cancer cells)
- Release of cancer cell antigens (cancer cell death)
- Killing of cancer cells (immune and cancer cells)

CTL = cytotoxic T cell.

Spontaneous anti-tumor T cell responses exist in cancer

- Antitumor T cells are present in patients with cancer prior to any treatment: blood and tumor

- The T cell responses are insufficient
Tumors use complex, overlapping mechanisms to evade and suppress the immune system

1. Inhibition of tumor antigen presentation
e.g. down regulation of MHC I

2. Secretion of immunosuppressive factors
 e.g. TGF-β

3. Inhibition of attack by immune cells
e.g. through T-cell checkpoint pathways

4. Recruitment of immunosuppressive cell types
 e.g. T-reg

MHC = major histocompatibility complex; TGF-β = tumor growth factor-β.

Take home messages

• p16+ oropharyngeal has a better outcome: de-escalation ongoing but NOT STANDARD today? Cetuximab?

• EGFR is prognosis

• Unfortunately, we are missing validated biomarkers and the treatment is still based on disease stage, tumor location, and centre expertise and not on tumor biology